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Synthesis of Sugar Derivatives of *N*-Methyl-*N*-nitrosourea

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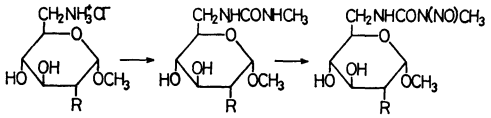
Streptozotocin is a broad spectrum antibiotic and possesses antitumor,[1,2] mutagenic,[3] and diabetogenic[2,4-9] activities. Its isolation from a fermentation broth of *Streptomyces achromogenes var. streptozoticus* was reported in 1960[10-13], and the structure has been established to be *N*-carbamyl-*N'*-methyl-*N'*-nitroso-D-glucosamine along with the synthesis.[14,15]

In previous papers, a synthesis of methyl glycosides of this antibiotic[16] and that of the analogs in which D-glucosamine was substituted for aminocyclitols[17] were described. In the present note, we wish to report the analogs of methyl 6-amino-6-deoxy-α-D-glucopyranoside and methyl 2,6-diamino-2,6-dideoxy-α-D-glucopyranoside.

Methyl 6-amino-6-deoxy-α-D-glucopyranoside hydrochloride (**1**)[18] and methyl 2,6-diamino-2,6-dideoxy-α-D-glucopyranoside dihydrochloride (**4**) were used as starting materials. **1** and **4** were treated with methyl isocyanate in the presence of silver carbonate giving respective *N*-carbamyl-*N'*-methyl derivatives (**2**) and (**5**) in 75 and 65% yield. Nitrosation of **2** and **5** were carried out with sodium nitrite in aqueous acetic acid to give *N*-nitroso derivatives (**3**) and (**6**) in 49 and 67% yield respectively. **3** and **6** were active against Ehrlich ascites tumor in mice.



1 R=OH 2 R=OH 3 R=OH
4 R=$NH_3^+Cl^-$ 5 R=NHCONHCH3 6 R=NHCON(NO)CH3

Experimental

General. Melting points were determined in capillary tubes and are uncorrected. Solutions were evaporated below 50°C under reduced pressure.

*Methyl 6-Amino-6-deoxy-α-D-glucopyranoside hydrochloride (**1**).* This compound was prepared by the method of Cramer.[18]

Methyl N-*Carbamyl*-N'-*methyl-6-amino-6-deoxy-α-D-glucopyranoside (**2**).* A 502 mg portion of **1** was dissolved in 65% aqueous acetonitrile (72 ml). To the solution, silver carbonate (363 mg) and methyl isocyanate (0.16 ml) were added and the mixture was heated for 1 hr under reflux. After cooling, the mixture was filtered and the filtrate was evaporated. The residue was crystallized in acetonitrile to give a crude product (426 mg, 78%). Recrystallization from *n*-propanol yielded crystals of mp 176—177°C. $[\alpha]_D^{22}$ +99° (*c* 1.0, methanol).

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Found: C, 42.91; H, 6.93; N, 11.13%. Calcd for $C_9H_{18}N_2O_6$: C, 43.19; H, 7.25; N, 11.20%.

Methyl N-*Carbamyl*-N′-*methyl*-N′-*nitroso*-6-*amino*-6-*deoxy*-α-D-*glucopyranoside* (**3**). **2** (120 mg) was dissolved in 5.6% aqueous acetic acid (18 ml) under ice cooling. 0.1 M Sodium nitrite solution (6.5 ml) was added to the solution and the mixture was settled overnight at room temperature. After sodium ions were removed by treating with Amberlite IR-120 (H^+ type), the solution was lyophilized. The residue was crystallized in ethanol under ice cooling to give the product (65 mg, 49%), mp 106—107°C. $[\alpha]_D^{22}$ +82.0° (*c* 0.5, methanol).

Found: C, 39.08; H, 6.20; N, 14.80%. Calcd for $C_9H_{17}N_3O_7$: C, 38.71; H, 6.14; N, 15.05%.

Methyl N-*benzyloxycarbonyl*-6-O-*tosyl*-α-D-*glucosaminide*. The product was prepared by the method of Foster *et al.*[19].

Methyl 2,6-*Diamino*-2,6-*dideoxy*-α-D-*glucopyranoside dihydrochloride* (**4**). A mixture of methyl *N*-benzyloxycarbonyl-6-*O*-tosyl-α-D-glucosaminide[19] (7.3 g) and sodium azide (5.4 g) in 70% aqueous 2-methoxyethanol (140 ml) was heated for 21 hr under reflux. The solution was evaporated and the residue was extracted with warm acetone. The acetone extracts were evaporated and the residue was hydrogenated in ethanol (55 ml) with 5% palladium on carbon and conc hydrochloric acid (1.7 ml) at 3.4 kg/cm² hydrogen pressure for 21 hr. After the catalyst was removed by filtration, the solution was evaporated to give a crude product (1.97 g, 49%), mp 198—201°C (decomp.). Recrystallization from ethanol-methanol gave hygroscopic crystals with the same decomposition point. $[\alpha]_D^{21}$ +125° (*c* 1.28, water). The product showed a ninhydrin-positive single spot on paper chromstography (R_f 0.26) in *n*-butanol-pyridine-water (6 : 4 : 3) system in an ascending development (R_f D-glucosamine hydrochloride 0.36).

Found: C, 31.59; H, 6.73; N, 10.56; Cl, 24.82%. Calcd for $C_7H_{18}N_2O_4Cl_2$: C, 31.71; H, 6.84; N, 10.57; Cl, 26.75%.

Methyl Di-N,N′-(N-*methyl*-*carbamyl*)-2,6-*diamino*-2,6-*dideoxy*-α-D-*glucopyranoside* (**5**). To a solution of **4** (911 mg) in 70% aqueous acetonitril (45 ml), methyl isocyanate (0.5 ml) and silver carbonate (1.4 g) were added and the mixture was heated for 1 hr under reflux. After cooling, the mixture was filtered and the filtrate was evaporated to give a crude product (684 mg, 65%). Recrystallization from ethanol afforded an analytically pure sample, mp 247—249°C. $[\alpha]_D^{22}$ +108° (*c* 0.88, water).

Found: C, 43.02; H, 7.30; N, 18.30%. Calcd for $C_{11}H_{22}N_4O_6$: C, 43.14; H, 7.24; N, 18.29%.

Methyl Di-N,N′-(N-*methyl*-N-*nitroso*-*carbamyl*)-2,6-*diamino*-2,6-*dideoxy*-α-D-*glucopyranoside* (**6**). **5** (684 mg) was treated with 0.5 M sodium nitrite solution (7.6 ml) in 5.7% aqueous acetic acid (26.5 ml) as described in **3**. After the solution was settled overnight, the crystals were collected by filtration to give a first crop of the product (338 mg), mp 154—156°C. The mother liquor was treated with Amberlite IR-120 (H^+ type) and then lyophilized. The residue was crystallized in ethanol to give a second crop of the product (204 mg), mp 154—156°C. Total yield was 67%. Recrystallization from methanol afforded a sepcimen for analysis, mp 154.5°C (decomp.). $[\alpha]_D^{22}$ +106° (*c* 0.75, methanol).

Found: C, 36.25; H, 5.66; N, 22.94%. Calcd for $C_{11}H_{20}N_6O_8$: C, 36.26; H, 5.53; N, 23.07%.

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